

Award Number: W81XWH-14-2-0173

TITLE: Efficacy Study of a Fully Implanted Neuroprosthesis for Functional Benefit to Individuals with Tetraplegia

PRINCIPAL INVESTIGATOR: P. Hunter Peckham

CONTRACTING ORGANIZATION: Case Western Reserve University  
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14. ABSTRACT We propose to complete a Phase II Clinical Trial to demonstrate the safety and efficacy of a fully-implanted neuroprosthesis to provide upper extremity function for individuals with cervical SCI. This study will utilize the "networked neuroprosthesis" (NNP). The NNP system is completely implanted, including all power, signal processing, stimulus generation, and electrodes. We expect that this advanced system will lead to increased regular use of the neuroprosthesis, with a subsequent positive impact on quality of life. The completion of this study will allow us to proceed to broad dissemination of advanced neuroprosthetic systems for the provision of motor function in SCI and similar diseases.					
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## **1. INTRODUCTION:**

We propose to complete a Phase II Clinical Trial to demonstrate the safety and efficacy of a fully-implanted neuroprosthesis to provide upper extremity function for individuals with cervical SCI. We have completed a clinical feasibility study of a neuroprosthesis that provides myoelectrically-controlled hand grasp to this population. That device utilized external powering and processing, requiring the subjects to have assistance in donning and doffing the neuroprosthesis. We have now completed the design of a fully-implanted, modular neuroprosthetic system, the “networked neuroprosthesis” (NNP). The NNP system is completely implanted, including all power, signal processing, stimulus generation, and electrodes. This eliminates the requirement of having to wear any external components taped to the skin in order to gain hand function, which has been a requirement of all upper extremity neuroprostheses to date. We expect that these advances will lead to increased regular use of the neuroprosthesis, with a subsequent positive impact on quality of life. We have completed the development of this technology and have established a full supply chain for manufacture of this system. Recent funding from the State of Ohio has been obtained to develop this technology within the required manufacturing practices necessary for a commercial implantable medical device. In conjunction with the development of the technology, we have also developed and implemented a complete marketing strategy that is specifically targeted for implantable devices in SCI, with the NNP hand system as the first product. Thus, we are now fully equipped and prepared to conduct a Phase II clinical trial of this technology to demonstrate safety and efficacy. The completion of this study will allow us to proceed to broad dissemination of advanced neuroprosthetic systems for the provision of motor function in SCI and similar diseases.

## **2. KEYWORDS:**

Neuroprosthesis  
Functional Electrical Stimulation  
Spinal Cord Injury  
Paralysis  
Rehabilitation  
Upper Extremity  
Implantable Medical Device  
Tetraplegia

## **3. ACCOMPLISHMENTS:**

### **What were the major goals of the project?**

The major goal of this proposal was to implement the NNP System with ten cervical level spinal cord injured subjects and evaluate the resulting improvement in upper extremity function. Compare functional abilities with and without the use of the neuroprosthesis. The outcome assessments are designed around two hypotheses regarding the advantages of the NNP:

- #1. We hypothesize that at least 70% of all subjects will demonstrate improved function compared to their baseline performance in one or more activities (primary outcome measure).
- #2. We hypothesize that the proportion of subjects demonstrating daily usage (7 days/week) of the NNP System will be significantly higher than the published rate of daily usage for the first generation neuroprosthesis.

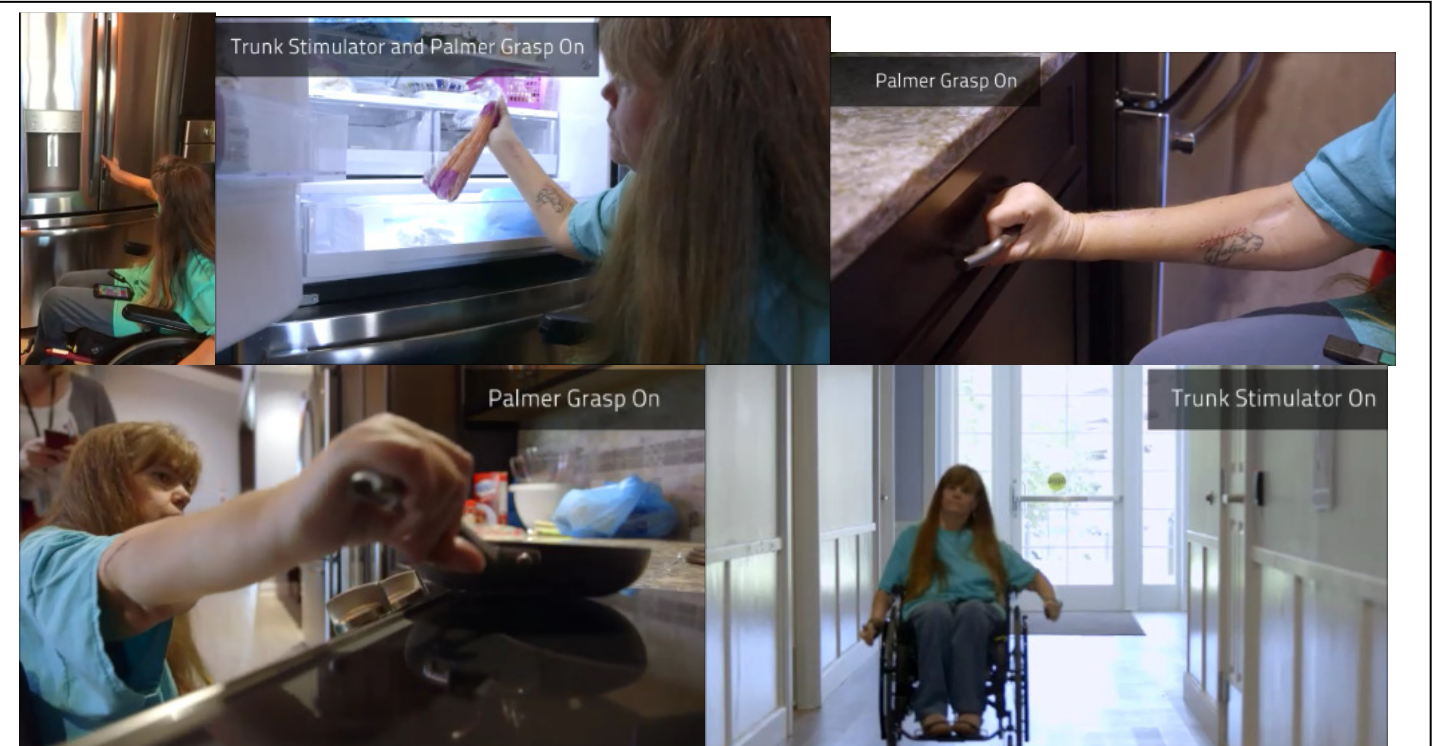
Project major tasks and milestones for the first 36 months of the project, showing percentage of completion as of 9/29/2017, on following page.

Major Task 1: Preparations and Support for Clinical Study	Months	% Completion	Notes
<b>Subtask 1: Prepare Regulatory Documents and Research Protocol</b>			
Coordinate Sites for IRB protocol submission at MHMC and LSVA	1	100%	
Submit screening protocol to IRB at MHMC and LSVA	2	100%	
Assemble response for IDE application to U.S. Food and Drug Administration (FDA)	1-5	100%	
Submit IDE response	5	100%	
Finalize consent form & human subjects protocol	5	100%	
Submit implantation protocol to IRB at MHMC and LSVA	5	100%	
Submit implantation protocol to HRPO	5	100%	
Assemble Clinical Events Committee	6	100%	
Submit amendments, adverse events and protocol deviations as needed	as needed		
<i>Milestone Achieved: Local IRB approval of Screening Protocol at MHMC and LSVA</i>	3	100%	
<i>Milestone Achieved: IDE approval from FDA</i>	7	100%	
<i>Milestone Achieved: Local IRB approval at MHMC and LSVA</i>	6	100%	
<i>Milestone Achieved: HRPO approval for all protocols</i>	7	100%	
<b>Subtask 2: Acquire Networked Neuroprosthesis Systems (NNP)</b>			
First round of purchases and assembly (3 systems)	6	100%	
Second round of purchases and assembly (3 systems)	12	50%	
<i>Milestone Achieved: NNP Systems received and sterilized</i>	7,13,17,21	33%	
Major Task 2: Conduct Clinical Study	Months	% Completion	Notes
<b>Subtask1: Subject Screening</b>			
Begin subject recruitment	6	100%	
Subject Screening	6-30	40%	
<i>Milestone Achieved: 1st participant consented and screened</i>	6	100%	
<i>Milestone Achieved: Study begins</i>	6	100%	
<b>Subtask2: NNP Implantation</b>			
Implant Subject #1	11	100%	[1]
Implant Subject #2	14	10%	
Implant Subject #3	17	0%	
Implant Subject #4	19	0%	
Implant Subject #5	21	0%	
<i>Milestones Achieved: Subjects implanted</i>	11-33	10%	
<b>Subtask3: Subject Assessment</b>			
Complete Outcomes Assessments with Subject #1	15	30%	
Complete Outcomes Assessments with Subject #2	19	0%	
Complete Outcomes Assessments with Subject #3	21	0%	
Complete Outcomes Assessments with Subject #4	23	0%	
Major Task 3: Data Analysis and Dissemination	Months		
<b>Subtask 1: Data Analysis</b>			
Perform all analyses according to specifications, share output and finding with all investigators	23-36	5%	
<i>Milestone Achieved: IDE annual report submission</i>	20,32	100%	
<b>Subtask 2: Data Dissemination</b>			
Presentation of results at national meetings	12-36	67%	
Preparation of manuscript #1 - first-in-man upper extremity NNP system case study	15	20%	
<i>Milestone Achieved: Manuscript #1 submitted</i>	18	0%	

### What was accomplished under these goals?

We have now successfully implanted the Networked Neuroprosthesis (NNP) System in three spinal cord injured subjects, including the first under SCIRP funding. These subjects are continuing to undergo training, functional evaluation, and follow-up. We are currently undertaking another round of manufacturing builds, which includes an updated circuit. When this is complete (quarter #2 of year 4) we will be able to continue implantation of NNP subjects to complete this study. Four subjects have completed their screening and are waiting for implantation scheduling.

Significant success has been achieved with the third subject to be implanted in a very short period of time. This subject has demonstrated multiple functional accomplishments, including opening a refrigerator, taking food out of a refrigerator, eating with a fork, holding a glass, improved posture, improved reach, and even improved wheelchair propulsion, as briefly outlined in Figure 1. This subject has reported daily usage of the system since returning from the initial rehabilitation period.



**Figure 1.** NNP #3 functional tasks, combining new function in hand grasp and trunk control. Top left: grasping refrigerator door handle and using trunk stimulation to stabilize trunk for opening. Top middle: getting a bag of carrots out of the refrigerator door. Top right: grasping and opening a drawer. Bottom left: hold a pan and moving it onto a stove surface. Bottom right: pushing a wheelchair using trunk stabilization.

### What opportunities for training and professional development has the project provided?

“Nothing to Report.”

### How were the results disseminated to communities of interest?

“Nothing to Report.”

### Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We will continue to perform NNP implants in new subjects. We expect to be slowed by the manufacturing rate throughout the project, but we still anticipate completing the proposed study during year 4. We are, at present, still meeting the modified subject implantation schedule that we described in our previous QPRs.

### 4. IMPACT:

#### What was the impact on the development of the principal discipline(s) of the project?

**Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project.**

We have demonstrated the power of a modular implantable system. Besides the obvious benefits of configurability with respect to multiple clinical applications, we have demonstrated the power of the modular approach to be resistant to component failures. Specifically, the modular approach provides significant functional redundancy. We have demonstrated that it is possible to surgically implant a modular system that extends essentially throughout the body – from upper thigh, torso, chest, arm, forearm, hand.

**What was the impact on other disciplines?**

Nothing to report.

**What was the impact on technology transfer?**

Nothing to report.

**What was the impact on society beyond science and technology?**

Nothing to report.

**5. CHANGES/PROBLEMS:****Changes in approach and reasons for change**

Our approach remains the same. However, as described previously, manufacturing procedures have caused a slowing of the implantation rate. However, we are now on track for the subject implantation uptake outlined in our previous QPRs.

**Actual or anticipated problems or delays and actions or plans to resolve them**

We have generally resolved the manufacturing delays and yield issues that we encountered in previous years, as evidenced by the implantation of our third subject. As described previously, we developed a mitigation strategy that included recruitment, scheduling logistics, surgical planning, overall study timeline, focus on study goals, and importance of subject follow-up to SCIRP study goals (see Annual report for Year 2 for details). We remain on-track at present and we continue to work with our manufacturing partners to try to improve yield and device inventory.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

**6. PRODUCTS:****Publications, conference papers, and presentations**

Nothing to report for 2017.

**Website(s) or other Internet site(s)**

<http://restorefunction.org/>

**Technologies or techniques**

Nothing to report.

**Inventions, patent applications, and/or licenses**

Nothing to report

**Other Products**

Nothing to report.

**7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS****What individuals have worked on the project?**

PI: P. Hunter Peckham

Others:

Anne Bryden  
Brian Smith  
Kevin Kilgore  
Megan Moynahan  
Michael Keith  
Harry Hoyen  
Greg Nemunaitis  
Ron Hart  
Antonia Wilson  
Alex Campean  
Betty Dungen

**Provide the name and identify the role the person played in the project.**

*If information is unchanged from a previous submission, provide the name only and indicate “no change”.*

Name: Hunter Peckham

No change in role, person months, or contribution from the original submission.

Name: Anne Bryden

No change in role, person months, or contribution from the original submission.

Name: Brian Smith

No change in role, person months, or contribution from the original submission.

Name: Kevin Kilgore

No change in role, person months, or contribution from the original submission.

Name: Megan Moynahan

No change in role, person months, or contribution from the original submission.

Name: Michael Keith

No change in role, person months, or contribution from the original submission.

Name: Harry Hoyer

No change in role, person months, or contribution from the original submission.

Name: Greg Nemunaitis

No change in role, person months, or contribution from the original submission.

Name: Betty Dunger

No change in role, person months, or contribution from the original submission.

Name: Antonia Wilson

No change in role, person months, or contribution from the original submission.

Name: Ron Hart

No change in role, person months, or contribution from the original submission.

Name: Mary Ann Richmond

No change in role, person months, or contribution from the original submission.

Name: Alex Campean

No change in role, person months, or contribution from the original submission.

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

**P. Hunter Peckham**

Two new grants started in the past year:

Grants started during this reporting period:

**Training of Activity of Muscles Below the Injury Level in Complete SCI for Neuroprosthetic Control (477004)**

Time Commitment: 0.44 calendar-months

Supporting Agency: Craig H. Neilsen Foundation

Grants Officer: Naomi Kleitman, Ph.D.

Performance Period: 07/31/17-07/30/2020

Funding: \$586,208 total

Goals and Aims: The first aim is to test a training sequence for improving the quality of below-injury signals that incorporates real-time visual biofeedback of generated EMG signals in a novel interactive visual interface which incorporates game-play. The second aim is to incorporate below-injury control sources into the control map for neuroprosthetic technology.

**Enhanced Modular Neuroprosthesis for the Restoration of Function in Neurological Injury or Disease (R01-EB-024522)**

Time Commitment: 1.64 calendar-months

Supporting Agency: NIH/NIBIB, Bethesda, MD

Grants Officer: Michael Wolfson, Ph.D.

Performance Period: 9/6/2017-5/31/2021

Funding: \$445,731/year



**Goals:** The goal of this study is to create, develop, and test the second generation networked neuroprosthesis, with enhanced functions and improved power and recharge capacity.

**Specific Aims:**

**Aim #1. Enhance Hardware.** We will improve power management in the NNP in order to significantly increase run time and decrease recharge time to improve system usability. Run time will be increased by a factor of five, making the system practical for continuous use. We will upgrade microprocessing power to further improve power efficiency, and significantly enhance user access and future software development while maintaining overall system safety and functionality. We will upgrade each module with a 9-axis motion tracking component, expanding the sensing functions available for clinical applications.

**Aim #2. Upgrade Software.** We will upgrade the software to take advantage of the upgraded microprocessors and to improve power efficiency. Programming upgrades will include improved interfaces for surgical installation, technical troubleshooting, and a MATLAB interface for research development.

**Aim #3. Build.** Design, layout, and build upgraded circuits; fabricate complete systems for testing.

**Aim #4. Test.** Test all aspects of the system for functional operation. Conduct electromagnetic compatibility and electrostatic discharge testing. Evaluate and address MRI compatibility.

**Overlap:** There is no scientific overlap between this grant and the proposed project.

**Kevin L. Kilgore**

Four new grants started in the past year:

Grants started during this reporting period:

**Enhanced Modular Neuroprosthesis for the Restoration of Function in Neurological Injury or Disease (R01-EB-024522)**

Time Commitment: 1.64 calendar-months

Supporting Agency: NIH/NIBIB, Bethesda, MD

Grants Officer: Michael Wolfson, Ph.D.

Performance Period: 9/6/2017-5/31/2021

Funding: \$445,731/year

**Goals:** The goal of this study is to create, develop, and test the second generation networked neuroprosthesis, with enhanced functions and improved power and recharge capacity.

**Specific Aims:**

**Aim #1. Enhance Hardware.** We will improve power management in the NNP in order to significantly increase run time and decrease recharge time to improve system usability. Run time will be increased by a factor of five, making the system practical for continuous use. We will upgrade microprocessing power to further improve power efficiency, and significantly enhance user access and future software development while maintaining overall system safety and functionality. We will upgrade each module with a 9-axis motion tracking component, expanding the sensing functions available for clinical applications.

**Aim #2. Upgrade Software.** We will upgrade the software to take advantage of the upgraded microprocessors and to improve power efficiency. Programming upgrades will include improved interfaces for surgical installation, technical troubleshooting, and a MATLAB interface for research development.

**Aim #3. Build.** Design, layout, and build upgraded circuits; fabricate complete systems for testing.

**Aim #4. Test.** Test all aspects of the system for functional operation. Conduct electromagnetic compatibility and electrostatic discharge testing. Evaluate and address MRI compatibility.

**Overlap:** There is no scientific overlap between this grant and the proposed project.

**Combined No-onset Waveform for Kilohertz Frequency Alternating Current Nerve Block (R01-EB-024860)**

Time Commitment: 0.44 calendar-months

Supporting Agency: NIH/NIBIB, Bethesda, MD

Grants Officer: Michael Wolfson, Ph.D.

Performance Period: 8/2/2017-4/30/2021

Funding: \$297,983/year

**Goals:** The purpose of this study is to develop and test a novel waveform that combines charge-balanced and charge-imbalanced waveforms to produce a kilohertz frequency nerve block that does not produce an onset response in the nerve.

**Specific Aims:**

**Aim 1:** Design and optimize the CNOW in simulations using FEM analysis of the electrodes and myelinated and unmyelinated computer neuron models.

**Aim 2:** Design and assemble robust hardware, software, and electrodes to deliver the CNOW.

**Aim 3:** Demonstrate and characterize the CNOW in-vivo. Test and optimize the CNOW in an acute rodent model (sciatic nerve and vagal nerve).

**Aim 4:** Evaluate the effectiveness of the CNOW for future clinical applications.

**A. Test and optimize the CNOW in autonomic nerves in an acute canine model (vagus and cardiac sympathetic) for cardiac applications.**

**B. Test and optimize the CNOW in autonomic nerves in ex-vivo guinea pig pulmonary nerves, for pulmonary applications.**

**Training of Activity of Muscles Below the Injury Level in Complete SCI for Neuroprosthetic Control (477004)**

Time Commitment: 0.44 calendar-months  
Supporting Agency: Craig H. Neilsen Foundation  
Grants Officer: Naomi Kleitman, Ph.D.  
Performance Period: 07/31/17-07/30/2020  
Funding: \$586,208 total

Goals and Aims: The first aim is to test a training sequence for improving the quality of below-injury signals that incorporates real-time visual biofeedback of generated EMG signals in a novel interactive visual interface which incorporates game-play. The second aim is to incorporate below-injury control sources into the control map for neuroprosthetic technology.

**The Northeast Ohio Regional Spinal Cord Injury Model System (90SI5025-01-00)**

Time Commitment: 0.26 calendar-months  
Supporting Agency: NIDILRR  
Grants Officer: Robert Jones, MD  
Performance Period: 9/30/16 to 9/29/21  
Funding: \$500,000/year

Goals: The goal of this study is to establish MetroHealth Medical Center as a Model System in Spinal Cord Injury, includes data collection into the national database, assessment of lower motor neuron damage in SCI, and development of an improved spine board.

**Michael W. Keith**

Nothing to report.

**Harry A. Hoyen**

Nothing to report.

**Greg Nemunaitis**

One new grant started this year:

**The Northeast Ohio Regional Spinal Cord Injury Model System (90SI5025-01-00)**

Time Commitment: 0.6 calendar-months  
Supporting Agency: NIDILRR  
Grants Officer: Robert Jones, MD  
Performance Period: 9/30/16 to 9/29/21  
Funding: \$500,000/year

Goals: The goal of this study is to establish MetroHealth Medical Center as a Model System in Spinal Cord Injury, includes data collection into the national database, assessment of lower motor neuron damage in SCI, and development of an improved spine board.

**Mary Ann Richmond**

Nothing to report.

**Megan Moynahan**

Nothing to report.

**Anne Marie Bryden**

One grant started during the past year.

**Training of Activity of Muscles Below the Injury Level in Complete SCI for Neuroprosthetic Control (477004)**

Time Commitment: 3.6 calendar-months  
Supporting Agency: Craig H. Neilsen Foundation  
Grants Officer: Naomi Kleitman, Ph.D.  
Performance Period: 07/31/17-07/30/2020  
Funding: \$586,208 total

Goals and Aims: The first aim is to test a training sequence for improving the quality of below-injury signals that incorporates real-time visual biofeedback of generated EMG signals in a novel interactive visual interface which incorporates game-play. The second aim is to incorporate below-injury control sources into the control map for neuroprosthetic technology.

**What other organizations were involved as partners?**

Nothing to Report.

**8. SPECIAL REPORTING REQUIREMENTS:**

QUAD CHART: In appendix.

## 9. APPENDICES: Quad Chart

### Efficacy Study of a Fully Implanted Neuroprosthesis for Functional Benefit to Individuals with Tetraplegia

SC130252

W81XWH-14-2-0173

PI: P. Hunter Peckham

Org: Case Western Reserve University, Cleveland, OH

Award Amount: \$2,363,423

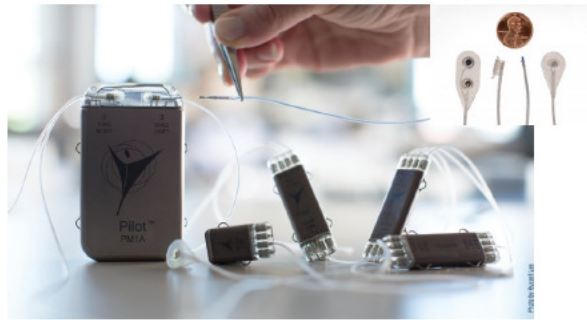


#### Study/Product Aim(s)

•Task #1 – Implement ten cervical level spinal cord injured subjects and evaluate the resulting improvement in upper extremity function. Compare functional abilities with and without the use of the neuroprosthesis.

#### Approach

The outcome assessments are designed around two hypotheses regarding the advantages of the Networked Neuroprosthesis (NNP): #1. We hypothesize that at least 70% of all subjects will demonstrate improved function compared to their baseline performance in one or more; and #2. We hypothesize that the proportion of subjects demonstrating daily usage of the NNP System will be significantly higher than the published rate of daily usage for the first generation neuroprosthesis.



Accomplishment: First subjects have been successfully implanted and have demonstrated functional use of the hand and trunk.

#### Timeline and Cost

Activities	PY	1	2	3	
Regulatory and Administrative					
Technology Acquisition					
Implantation of NNP					
Assessment of Outcomes					
Estimated Budget (\$K)		\$792	\$446	\$262	\$000

Updated: Oct. 30, 2017

#### Goals/Milestones (Example)

**PY1 Goal** – Complete Regulatory; Acquire first systems, First implant

☒ IDE

☒ Acquire first systems (100% complete)

**PY2 Goals** – System Implantation and Evaluation

✓ Acquire technology (30% complete)

✓ System Implantation (10% complete)

☐ System Evaluation – Functional Assessments

**PY3 Goal** – System Implantation and Evaluation

☐ System Implantation

☐ System Evaluation – Functional Assessments

**Comments/Challenges/Issues/Concerns**

• Encountered manufacturing yield issues and slow procedures.

• Delay- initial surgeries – still expect to complete project in 4 years.

**Budget Expenditure to Date**

Projected Expenditure: \$1.23M

Actual Expenditure: \$1.1M